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(PCT Article 36 and Rule 70)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

Applicant's or	agent's file reference		See Notifi	ication of Transmittal of International
PP/NT/PH/3281		FOR FURTHER ACTIO	N Prelimina	ry Examination Report (Form PCT/IPEA/416)
International	application No.	International filing date (day/r	nonth/year)	Priority date (day/month/year)
PCT/GB99	0/00968	26/03/1999		27/03/1998
International C12Q1/68	Patent Classification (IPC) or na	tional classification and IPC		
Applicant				
ISIS INNO	VATION LIMITED et al.		, <u></u> ,	
 This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36. 				
2. This R	EPORT consists of a total of	f 8 sheets, including this co	ver sheet.	
This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT). These annexes consist of a total of 2 sheets.				
3. This re	port contains indications rel	ating to the following items:		
1	☑ Basis of the report			
11	☐ Priority			
III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability				
IV	Lack of unity of invent			
V	 Neasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement 			
VI	Certain documents ci	ted		
VII	Certain defects in the	international application		
VIII	☐ Certain observations	on the international applicati	on	
Date of subr	mission of the demand	D	ate of completion	of this report
27/10/1999		oz	02.06,2000	

Authorized officer

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preliminary examining authority:



INTERNATIONAL PRELIMINARY EXAMINATION REPORT



International application No. PCT/GB99/00968

I.	Basis	of the	report
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	-				
1.	This report has been drawn on the basis of (substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.):				
	Description, pages:				
	1-12	as originally	filed		
	Claims, No.:			•	
	1-14	with telefax	of	25/04/2000	
2.	The amendments hav	re resulted in t	ne cancel	llation of:	
	☐ the description,	pages:			
	☐ the claims,	Nos.:			
	☐ the drawings,	sheets:			
3.				some of) the amendments had not been made, since they have been as filed (Rule 70.2(c)):	
4.	Additional observation	ns, if necessar	y:		
V.	Reasoned statemen applicability; citation	t under Articl ns and explar	e 35(2) w nations s	vith regard to novelty, inventive step or industrial supporting such statement	
1.	Statement				
	Novelty (N)	Yes: No:	Claims Claims		
	Inventive step (IS)	Yes: No:	Claims Claims		
	Industrial applicability	(IA) Yes:	Claims		



INTERNATIONAL PRELIMINARY EXAMINATION REPORT



International application No. PCT/GB99/00968

2. Citations and explanations

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet





INTERNATIONAL PRELIMINARY International application No. EXAMINATION REPORT - SEPARATE SHEET

PCT/GB99/00968

ITEM V:

- 1. Reference is made to the following documents:
- D1 ABRAMSON ET AL, PUBLIC HEALTH REVIEW, vol. 26, no. 2, February 1998, pages 127-144
- D2 DATABASE CHEMABS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US1997 GCGA, STN Database accession no. 126:273057 & NAT. GENET. (1997), 15(4), 389-392, 1997
- D3 DANIELS ET AL, NATURE, vol. 383, 1996, pages 247-50
- D4 Asthma Gene Database, server http://cooke.csf.de/asthmagen/db/show.clm Main Tables, chr. 2, linkage table p < 0.5, cited by the applicant
- 2. Industrial applicability (Art. 33(4) PCT):

The subject-matter of claims 1-14 is susceptible of industrial application.

3. Novelty (Art. 33(2) PCT):

D1 reviews the state of the art of asthma related genetic markers and summarizes the results obtained in D2 and D3. The following regions of interest have been exemplified in D1 and D2 or D1 and D3: chromosomes 2q33, 4, 5p15, 6, 7, 11p15, 13, 16, 17p11.1-q11.2, 19q13 and 21q21 (see D1, abstract and page 137, last paragraph, Table 2; see D2, abstract and D3, tables 1 and 2). Only D1 and D2 disclose a asthma-related chromosome 2 region.

The region 2q33 which is associated with asthma as shown in D1 and D2 would appear to be different from the region claimed in claim 1 of the present application, since the D1/D2 regions listed in document D4 under the heading Collaborative 1997 are all located on chromosome 2 at a distance superior to 1 Mb/cM from the locus D2S308.

The subject-matter of claim 1 is therefore novel over D1/D2. It follows that claims 2-9





INTERNATIONAL PRELIMINARY InterEXAMINATION REPORT - SEPARATE SHEET

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meet the requirements for novelty.

Concerning claims 10-14, it should be noted that the unclear definition of the sequences, i.e. by the result to be achieved or using the wording "substantially similar sequences" (see section VIII, below), does not make the intended limitations clear. Since the sequences claimed are not clearly defined, the objection for lack of novelty is maintained by this Authority. It cannot at present be excluded that the sequences implicitly disclosed in D1/D2 do not fall within the scope of claims 10-14 (see the PCT Guidelines, Gazette PCT-Section IV, IV-7.5). The said claims are therefore not regarded as novel (Art. 33(2) PCT).

4. Inventive step (Art. 33(3) PCT):

D1-D3 are considered as the closest prior art documents.

Claim 1 is directed to a nucleic-acid based method for diagnosing asthma or a predisposition to asthma.

D1-D3 all disclose nucleic-acid based methods for diagnosing asthma or detecting a predisposition to asthma.

The problem solved by claim 1 over the cited prior art can be seen as the provision of an alternative method for predicting susceptibility to asthma (cf. description of the present application, page 10, lines 15-18).

The solution proposed in claim 1 consists in demonstrating the presence or absence of an allele which is associated with asthma, wherein the allele is situated at a locus in a region of chromosome 2 of up to 1 megabase in length, which region contains the locus D2S308.

This solution is regarded as inventive, because none of the cited prior art document suggests that this particular region could play a role in asthma. Claim 1 does therefore satisfy the requirements of Article 33 (3) PCT. It follows that claims 2-9 meet also the requirements for inventiveness.





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ITEM VII:

1. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1/D2 are not mentioned in the description, nor are these documents identified therein.

ITEM VIII:

- 1. Claims 1-6, 8, 10-12 and 14 broadly define the following features in terms of their function:
 - (i) Claims 1-6, 8: "which method comprises demonstrating in the individual the presence or absence of **an allele** which is associated with asthma, wherein the allele is situated at a locus in a region of chromosome 2 of up to 1 megabase in length, which region contains the locus D2S308".
 - (ii) Claims 10-12, 14: "primers for amplification of an allele "and primers capable of hybridising under suitable stringent conditions to a region either side of a region of microsatellite repeats at D2S308"

However, the description convey the impression that these functions can only be carried out in a particular way, namely by (i) amplifying the allele D2S308*3 (see page 10, description of the present application) with the (ii) primers SEQ ID NO:1 and 2 (see pages 7 and 8, description of the present application), and no alternative means are envisaged.

It is clear that the examples of a patent application do not have to be exhaustive (Rule 5.1 v) PCT) and that the claims must be formally supported by the description of the application. However, Article 6 PCT states that the claims must be fully supported by the description, i.e the support must be both formal and technical, as indicated in the PCT Guidelines, Gazette PCT-Section IV, III-6.3. While there is certainly a formal support in the description for the said claims, it is considered that the technical support provided and which would be necessary to enable the extension of the particular teaching of the description to the whole of the field claimed is not sufficient. More specifically, it is noted that in the cited prior





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art, the identification of asthma-related loci has been carried out, i.e large region of genomic DNA have been identified as asthma-related. Moreover, the identification of specific genes is considered to be "a significant discovery" (see D1, page 131, 1st paragraph) by the skilled person.

Consequently, the identification of specific alleles associated with asthma does not seem to be a trivial task, even for the skilled person, even when the locus is known.

When applied to the present application, this analysis of the prior art apparently leads to the conclusion that claim 1 which claims a method for detecting every allele associated with asthma, moreover within a big region of 1 to 2 Mb flanking the locus D2S308, is not fully supported by the description, because the whole of the field claimed cannot apparently be reproduced using routine methods or experimentation, as indicated by the highly skilled person working in the field.

Consequently, the same objection arises for claims directed to primers to be used in said methods.

Hence, claims 1-6, 8, 10-12 and 14 are not supported by the description as required by Article 6 PCT.

- The relative definition of the region of claims 1 and 10 (up to 1 megabase in 2. length) leaves the reader in doubt as to the extent of protection claimed, especially in the light of the description of the present application, page 3, lines 1-4: page 4, lines 16-17. It should have been clearly indicated in the claims, as it has been done in the description, where the said region starts and finishes by giving a precise reference point (see the PCT Guidelines, PCT Gazette-Section IV, III-4.1). This defect renders the definition of the subject-matter of said claims unclear (Article 6 PCT), because the location of the allele and/or of the D2S308 locus within the 1 Mb region is/are not precisely indicated. A clarification of the claim would not appear to render the claim unwieldy.
- Claims 10 and 12 do not meet the requirements of Article 6 PCT in that the matter 3. for which protection is sought is not clearly defined. The claims attempt to define the subject-matter in terms of the result to be achieved which merely amounts to a statement of the underlying problem:





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Claim 10: "A pair of oligonucleotide primers for amplification of an allele which is associated with asthma"

Claim 12: "..capable of hybridising under suitably stringent condition to a region either side of microsatellite repeats at D2S308"

The technical features necessary for achieving this result i.e. the nucleotide sequences should be added (cf. PCT Guidelines, PCT Gazette-Section IV, III-4.7). Again, it is considered that the result to be achieved (designing the primers) does involve more than trial and error, for the same reasons as under section VIII, item 1. Additionally and as indicated in the introductory portion above, the matter for which protection is sought is not clearly defined, because the primers are defined by a reference to the sequence to be amplified which is itself not precisely delimited (see Section VIII, item 2). The intended limitations are therefore not clear from claims 10 and 12 (Art. 6 PCT and PCT Guidelines, Gazette PCT-Section IV, III-4.8a).

4. The wording "substantially similar sequences" used in claim 9 and 13 is vague and unclear and leaves the reader in doubt as to the nucleotide sequences claimed, thereby rendering the definition of the subject-matter of said claim unclear (Article 6 PCT).

CY. VON: EPA-MUENCHEN 02





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CLAIMS

- 1. A method for diagnosing an individual as being asthmatic, or as having a predisposition to asthma, which method comprises demonstrating in a nucleic acid sample taken from an individual the presence or absence of an allele which is associated with asthma, wherein the allele is situated at a locus in a region of chromosome 2 of up to 1 megabase in length, which region contains the locus D2S308.
- The method according to claim 1, wherein the method comprises the steps of:
 - (i) providing a suitable tissue sample from the individual;
 - (ii) preparing from the tissue sample a nucleic acid sample;
 - (iii) analysing the nucleic acid sample for the presence or absence of the allele.
- 3. The method according to claim 2, wherein prior to analysis, the locus at which the allele is situated is amplified.
- 4. The method according to claim 3, wherein the amplification is by the PCR.
- 5. The method according to any one of claims 1 to 4, wherein the locus at which the allele is situated comprises microsatellite repeats of variable lengths.
- 6. The method according to claim 5, wherein amplification is performed using a pair of primers each of which hybridizes under suitably stringent conditions to a region either side of the microsatellite repeats.
- 7. The method according to any one of claims 1 to 6, wherein the allele for identification is D2S308*3.

25-04-2000





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- 8. The method according to any one of claims 3 to 7, wherein the analysis is carried out by size separation of amplification products.
- The method according to claim 6, wherein the primers in the pair of primers comprise the oligonucleotide sequences identified by SEQ ID NO: 1 and SEQ ID NO: 2 or substantially similar sequences.
- 10. A pair of oligonucleotide primers for amplification of an allele which is associated with asthma, which allele is situated at a locus in a region of chromosome 2 of up to 1 megabase in length, which region contains the locus D2S308.
- 11. The pair of oligonucleotide primers according to claim 10, one of which is labelled with a detectable marker.
- 12. The pair of oligonucleotides according to claim 10 or claim 11, capable of hybridising under suitably stringent conditions to a region either side of a region of microsatellite repeats at D2S308.
- 13. The pair of oligonucleotide primers according to claim 12, comprising the oligonucleotide sequences identified by SEQ ID NO: 1 and SEQ ID NO: 2 or substantially similar sequences.
- 14. An assay kit which comprises the pair of oligonucleotide primers according to any one of claims 10 to 13.

Copy for the Elected Office (EO/US)



PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

WILKINSON, Stephen, John Stevens, Hewlett & Perkins Halton House 20/23 Holborn London EC1N 2JD

	ROYAUME-UNI
Date of mailing (day/month/year)	
25 April 2000 (25.04.00)	
A. U. al	
Applicant's or agent's file reference	IMPORTANT NOTIFICATION
KP/3281 PCT	
International application No.	International filing date (day/month/year)
PCT/GB99/00968	26 March 1999 (26.03.99)
1. The following indications appeared on record concerning:	
the applicant the inventor	the agent the common representative
	State of Nationality State of Residence
Name and Address	State of Nationality State of Noside 1100
WILKINSON, Stephen, John Stevens, Hewlett & Perkins	T. L. L. L. M.
1Serjeants' Inn	Telephone No.
Fleet Street	+44 171 936 2499
London EC4Y 1NT United Kingdom	Facsimile No.
Gilliga Killigaolii	+44 171 936 2498
	Teleprinter No.
2. The International Bureau hereby notifies the applicant that the	ne following change has been recorded concerning:
the person the name X the add	
the person the name X the add	
Name and Address	State of Nationality State of Residence
WILKINSON, Stephen, John	
Stevens, Hewlett & Perkins Halton House	Telephone No.
20/23 Holborn	+44 20 7404 1955
London EC1N 2JD	Facsimile No.
United Kingdom	+44 20 7404 1844
	Teleprinter No.
3. Further observations, if necessary:	
3. Further observations, if necessary.	·
4. A copy of this notification has been sent to:	
X the receiving Office	the designated Offices concerned
the International Searching Authority	X the elected Offices concerned
	other:
X the International Preliminary Examining Authority	
	Authorized officer
The International Bureau of WIPO 34, chemin des Colombettes	Anman QIU
1211 Geneva 20, Switzerland	Aiilliali QiO

Telephone No.: (41-22) 338.83.38

Facsimile No.: (41-22) 740.14.35 Form PCT/IB/306 (March 1994)

FIENT COOPERATION TREAT

	From the INTERNATIONAL BUREAU
PCT	То:
NOTIFICATION OF THE RECORDING OF A CHANGE (PCT Rule 92bis.1 and Administrative Instructions, Section 422) Date of mailing (day/month/year)	CORNISH, Kristina Kilburn & Strode 20 Red Lion Street London WC1R 4PJ ROYAUME-UNI
31 October 2000 (31.10.00) Applicant's or agent's file reference	
KP/3281 PCT	IMPORTANT NOTIFICATION
International application No. PCT/GB99/00968	International filing date (day/month/year) 26 March 1999 (26.03.99)
The following indications appeared on record concerning: The applicant the inventor	the agent the common representative
Name and Address	State of Nationality State of Residence GB GB
ISIS INNOVATION LIMITED 2 South Parks Road Oxford OX1 3UB United Kingdom	Telephone No.
	Facsimile No.
	Teleprinter No.
2. The International Bureau hereby notifies the applicant that t	he following change has been recorded concerning:
the person the name X the add	
Name and Address ISIS INNOVATION LIMITED	State of Nationality State of Residence
Ewert House Ewert Place	Telephone No.
Summertown Oxford OX2 7BZ United Kingdom	Facsimile No.
v	Teleprinter No.
3. Further observations, if necessary:	
4. A copy of this notification has been sent to:	
X the receiving Office	the designated Offices concerned
the International Searching Authority	X the elected Offices concerned
the International Preliminary Examining Authority	other:
The International Bureau of WIPO	Authorized officer
34, chemin des Colombettes 1211 Geneva 20, Switzerland	Peggy Steunenberg
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38



PATENT	COOPERATION	TREATT

	From the INTERNATIONAL BUREAU
PCT	To:
NOTIFICATION OF THE RECORDING	
OF A CHANGE	CORNISH, Kristina
OFACIIANGE	Kilburn & Strode
(PCT Rule 92bis.1 and	20 Red Lion Street
Administrative Instructions, Section 422)	London WC1R 4PJ
, diffinistrative metrations, desiron 422	ROYAUME-UNI
Date of mailing (day/month/year)	1
29 September 2000 (29.09.00)	
Applicant's or agent's file reference	
KP/3281 PCT	IMPORTANT NOTIFICATION
I have all a little at the state of the stat	
International application No.	International filing date (day/month/year)
PCT/GB99/00968	26 March 1999 (26.03.99)
1. The following indications appeared on record concerning:	
the applicant the inventor	the agent the common representative
Name and Address	State of Nationality State of Residence
WILKINSON, Stephen, John	
Stevens, Hewlett & Perkins	Telephone No.
Halton House	+44 20 7404 1955
20/23 Holborn London EC1N 2JD	(1 - 2 - 1 - 1 - 1 - 1 - 1 - 1 - 1 - 1 -
United Kingdom	Facsimile No.
•	+44 20 7404 1844
	Teleprinter No.
2. The International Bureau hereby notifies the applicant that the	ne following change has been recorded concerning:
X the person the name the add	
Name and Address	State of Nationality State of Residence
CORNISH, Kristina	,*
Kilburn & Strode 20 Red Lion Street	Telephone No.
London WC1R 4PJ	+44 20 7539 4200
United Kingdom	Facsimile No.
	+44 20 7539 4299
	Teleprinter No.
	releprinter No.
3. Further observations, if necessary:	
	· **
4. A copy of this notification has been sent to:	
X the receiving Office	the designated Offices concerned
the International Searching Authority	X the elected Offices concerned
the International Preliminary Examining Authority	other:
	Authorized officer
The International Bureau of WIPO 34, chemin des Colombettes	
1211 Geneva 20, Switzerland	Jean-Marie McAdams
Ecosimila No : (41 32) 740 14 35	Talanhana Na . (41 22) 220 22 20





PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

WILKINSON, Stephen, John Stevens, Hewlett & Perkins 1 St. Augustine's Place Bristol BS1 4UD ROYAUMF-UNI

	ROYAUME-UNI
Date of mailing (day/month/year)]
03 February 2000 (03.02.00)	
Applicant's or agent's file reference	
KP/3281 PCT	IMPORTANT NOTIFICATION
International application No.	International filing date (day/month/year)
PCT/GB99/00968	26 March 1999 (26.03.99)
The following indications appeared on record concerning:	
	the agent the common representative
Name and Address	State of Nationality State of Residence
PRIVETT, Kathryn, Louise Stevens, Hewlett & Perkins	
1 Serjeants' Inn	Telephone No.
Fleet Street London EC4Y 1NT	0171 936 2499
United Kingdom	Facsimile No.
	0171 936 2498
3 °	Teleprinter No.
2. The International Bureau hereby notifies the applicant that the	ne following change has been recorded concerning:
X the person the name X the add	ress the nationality the residence
Name and Address	State of Nationality State of Residence
WILKINSON, Stephen, John	·
Stevens, Hewlett & Perkins 1 St. Augustine's Place	Telephone No.
Bristol BS1 4UD	0171 922 6007
United Kingdom	Facsimile No.
	0171 922 6009
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3. Further observations, if necessary:	
4. A copy of this notification has been sent to:	
X the receiving Office	the designated Offices concerned
the International Searching Authority	X the elected Offices concerned
X the International Preliminary Examining Authority	other:
	Authorized officer
The International Bureau of WIPO	Additional Officer

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland

S. Cruz

Facsimile No.: (41-22) 740.14.35

Telephone No.: (41-22) 338.83.38



PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents United States Patent and Trademark Office Box PCT Washington, D.C.20231 ÉTATS-UNIS D'AMÉRIQUE

Date of mailing (day/month/year)
03 December 1999 (03.12.99)

International application No.
PCT/GB99/00968

International filing date (day/month/year)
26 March 1999 (26.03.99)

Applicant

COOKSON, William, Osmond, Charles, Michael et al

ı		
	1.	The designated Office is hereby notified of its election made:
		X in the demand filed with the International Preliminary Examining Authority on:
l		27 October 1999 (27.10.99)
		in a notice effecting later election filed with the International Bureau on:
	2.	The election X was
		was not
		made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).
۱		

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland

Authorized officer

J.M. Vivet

Telephone No.: (41-22) 338.83.38